

FIAT LUX ET LUX EST

Le traiettorie di salute
Torino (TO) - 7 giugno 2025

IN HOC SIGNO VINCES

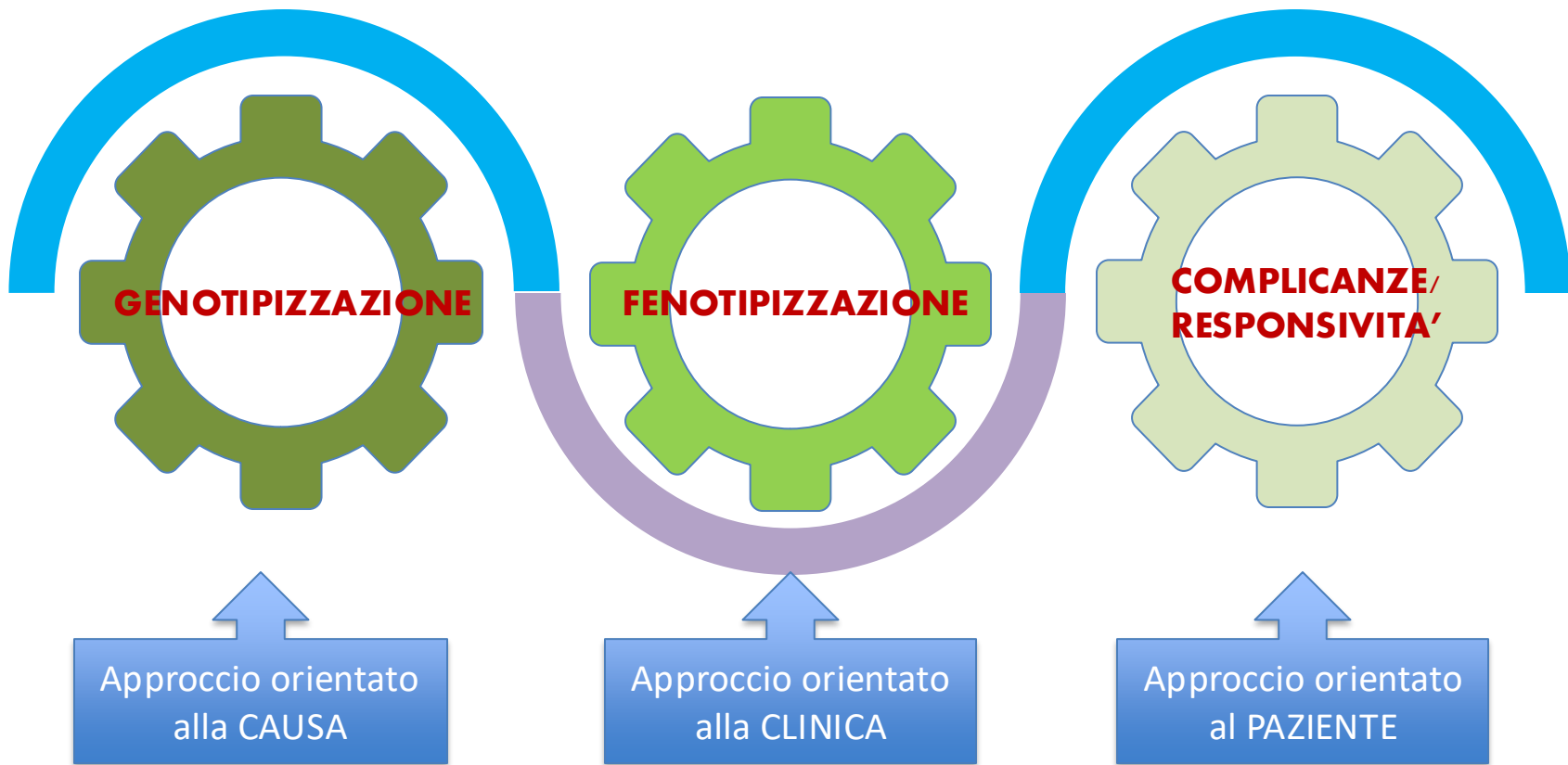
Strategie culturali-sociali e terapeutiche per la salute metabolica
Bra, Località POLLENZO (CN) - 22 novembre 2025

Ad ogni obesità il suo farmaco (?)

Paolo Marzullo

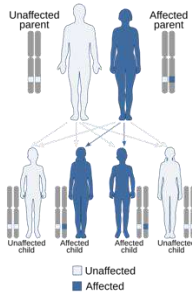
Endocrinologia, AOU Maggiore e Università del Piemonte Orientale

Novara

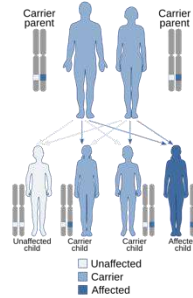


Disturbi mendeliani legati a obesità sindromica

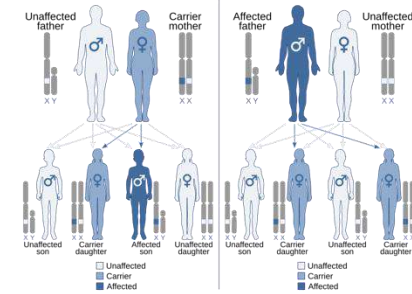
Autosomal dominant



Autosomal recessive



X-linked recessive



Autosomal Dominant Inheritance

Achondroplasia (ACH)

Albright hereditary osteodystrophy

Angelman syndrome

Insulin resistance syndromes

Posterior polymorphous corneal dystrophy

Familial partial lipodystrophy Dunnigan

Prader Willi syndrome

Thyroid hormone resistance syndrome

Ulnar-mammary syndrome

Autosomal Recessive Inheritance

Alstrom syndrome

Bardet-Biedl syndrome

Berardinelli-Seip cong. lipodystrophy

Cohen syndrome

Carbohydrate defic. glycoprot. type 1a

Fanconi-Bickel syndrome

Isolated growth hormone deficiency

Combined pituitary hormone deficiency

X-linked Inheritance

Borjeson-Forssman-Lehmann syndrome

Chroroderemia

Mehmo syndrome

Mental retardation X-linked, syn. 7

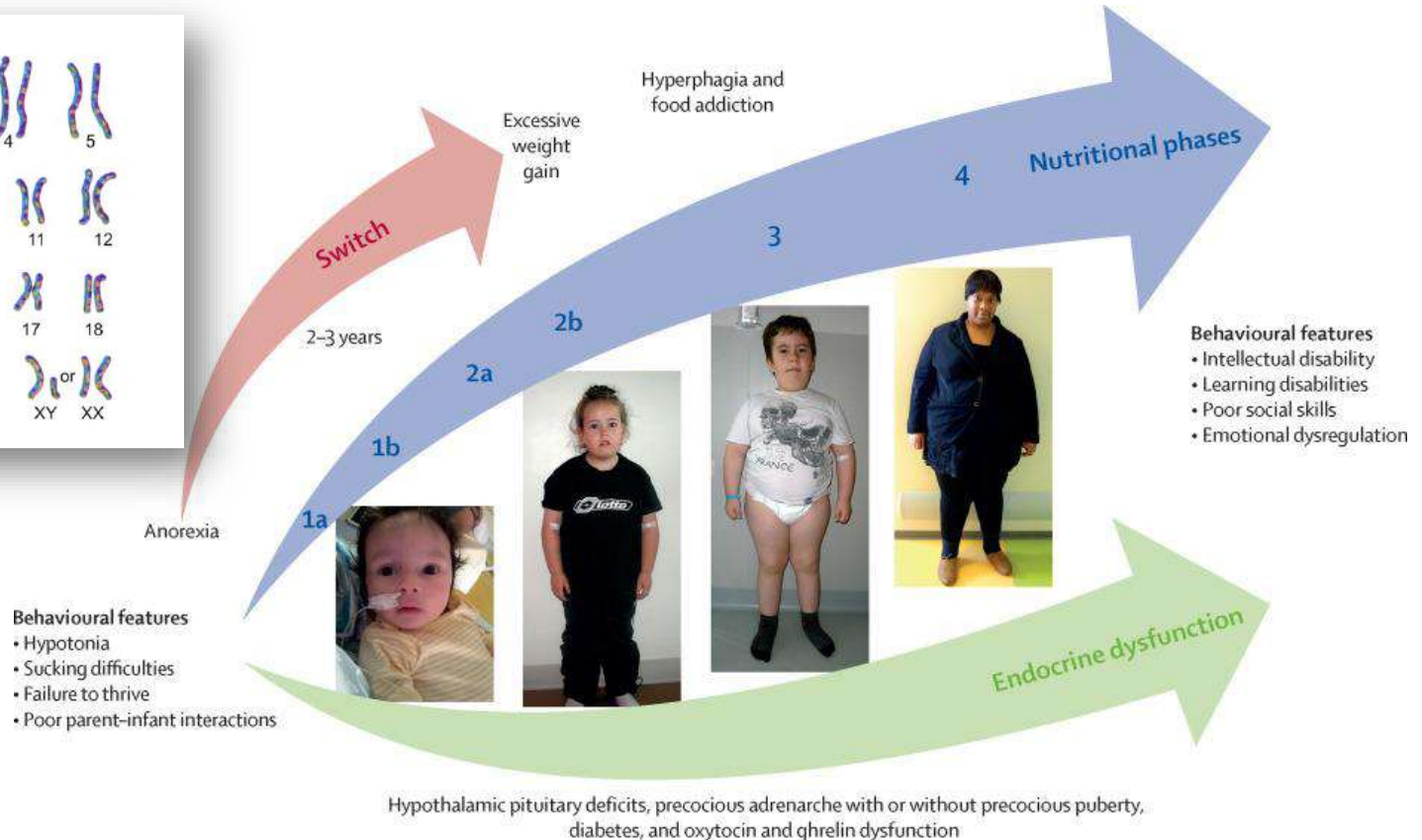
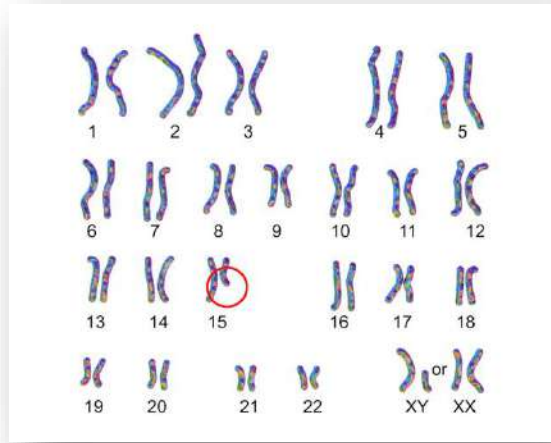
Prader-Willi-like syndrome

Shashi X-linked mental retardation syndrome

Simpson-Golabi-Behmel

Wilson-Turner syndrome

Obesità sindromica: la sindrome di Prader-Willi

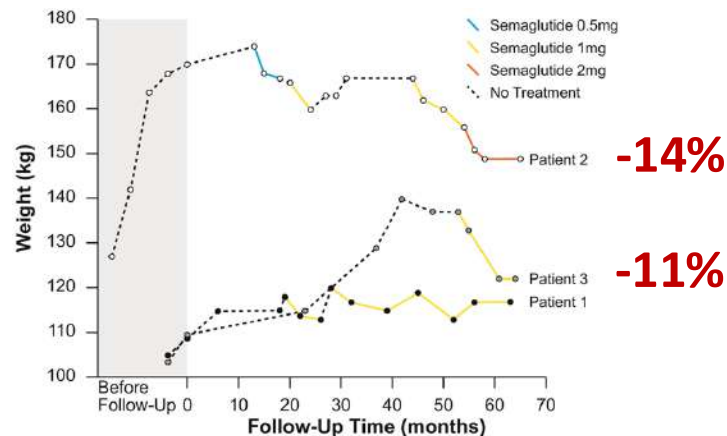
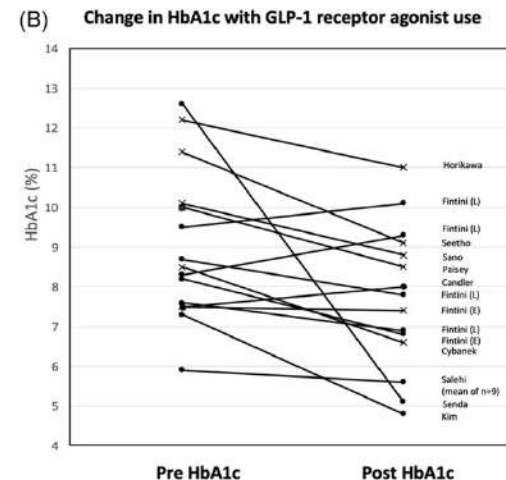
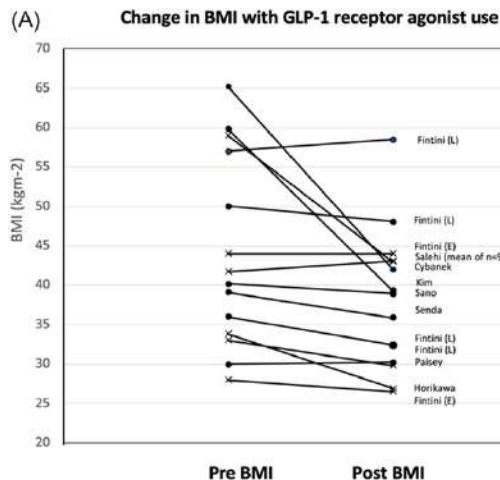


Uso di GLP1-RA nella sindrome di Prader-Willi

- 10 studi su 23 pazienti con PWS (exenatide n=4; liraglutide n=9)

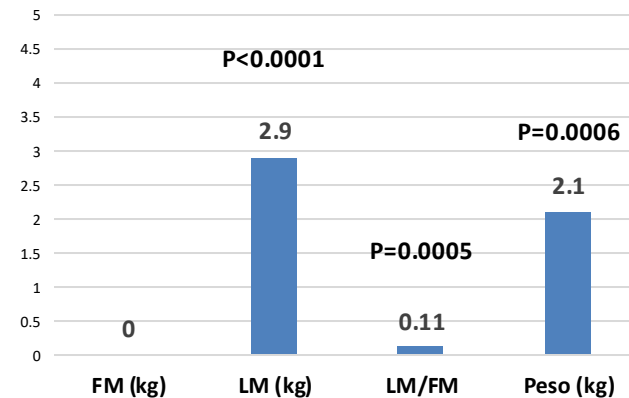
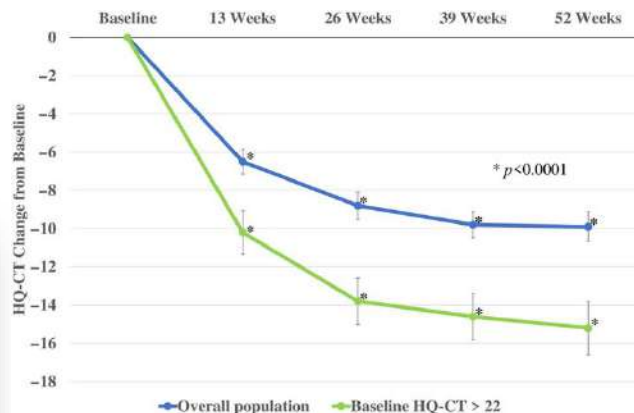
- Miglioramento del BMI in 10 (da -1,5 a -16,0 kg/m²)

- Miglioramento dei livelli di sazietà.

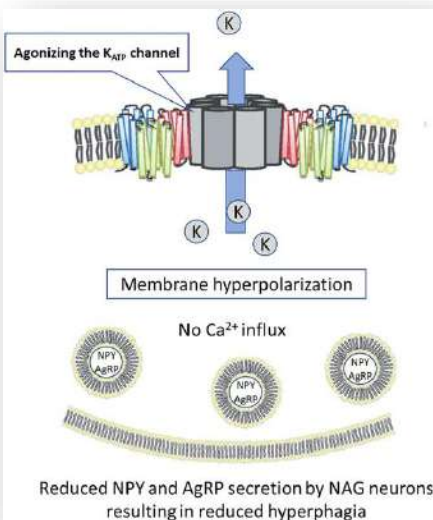


Diazossido di colina nella sindrome di Prader-Willi

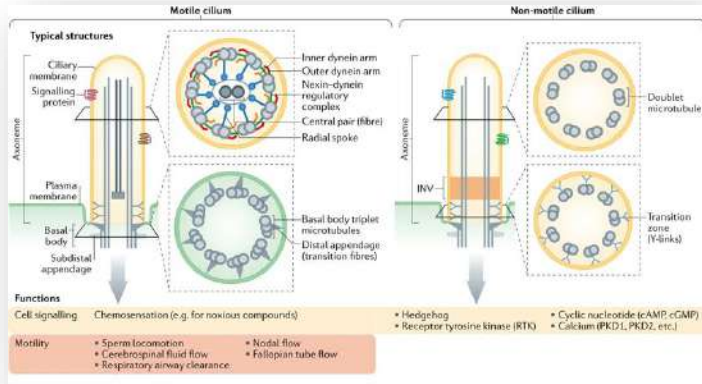
FDA-approved (26/03/2025)



- Miglioramenti significativi e clinicamente rilevanti dell'iperfagia.
- Miglioramenti significativi in altre complicanze comportamentali.
- Riduzioni significative della gravità della malattia.



Obesità sindromica: Sindrome di Bardet-Biedl



L'alterazione della segnalazione ciliare nella via del recettore della melanocortina-4 (MC4R) può contribuire all'obesità nella sindrome di Bardet-Biedl (BBS) o nella sindrome di Alström



ii. Diagnostic features

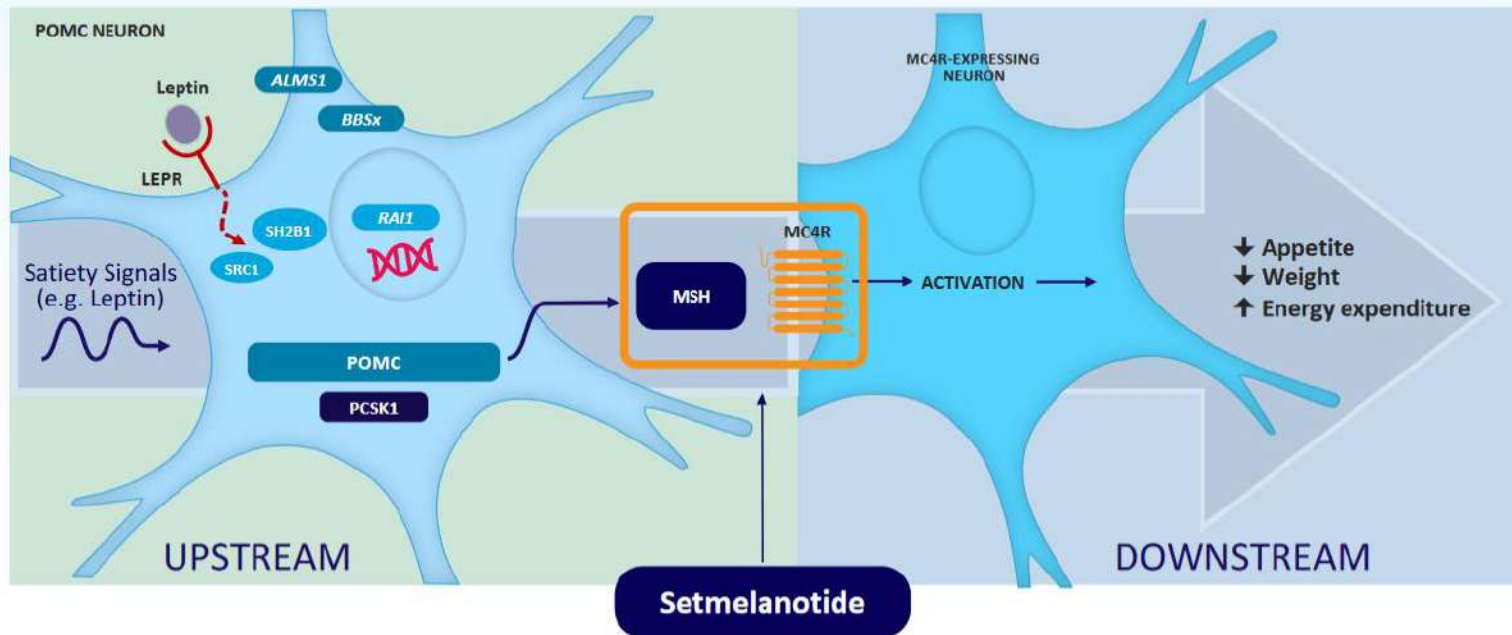
Primary features

	Frequency
Rod-cone dystrophy	93%
Polydactyly	63–81%
All four limbs:	21%
Upper limbs only:	9%
Lower limbs only:	21%
Obesity	72–92%
Genital anomalies	59–98%
Renal anomalies	53%
Learning difficulties	61%

Secondary features

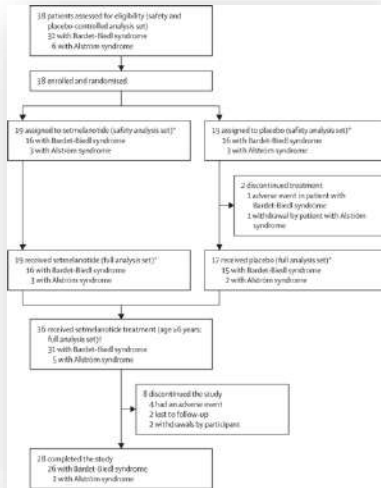
	Frequency
Speech delay	54–81%
Developmental delay	50–91%
Diabetes mellitus	6–48%
Dental anomalies	51%
Congenital heart disease	7%
Brachydactyly/ syndactyly	46–100%/8–95%
Ataxia/ poor coordination	40–86%
Anosmia/hyposmia	60%

Alterazioni del pathway di MC4R

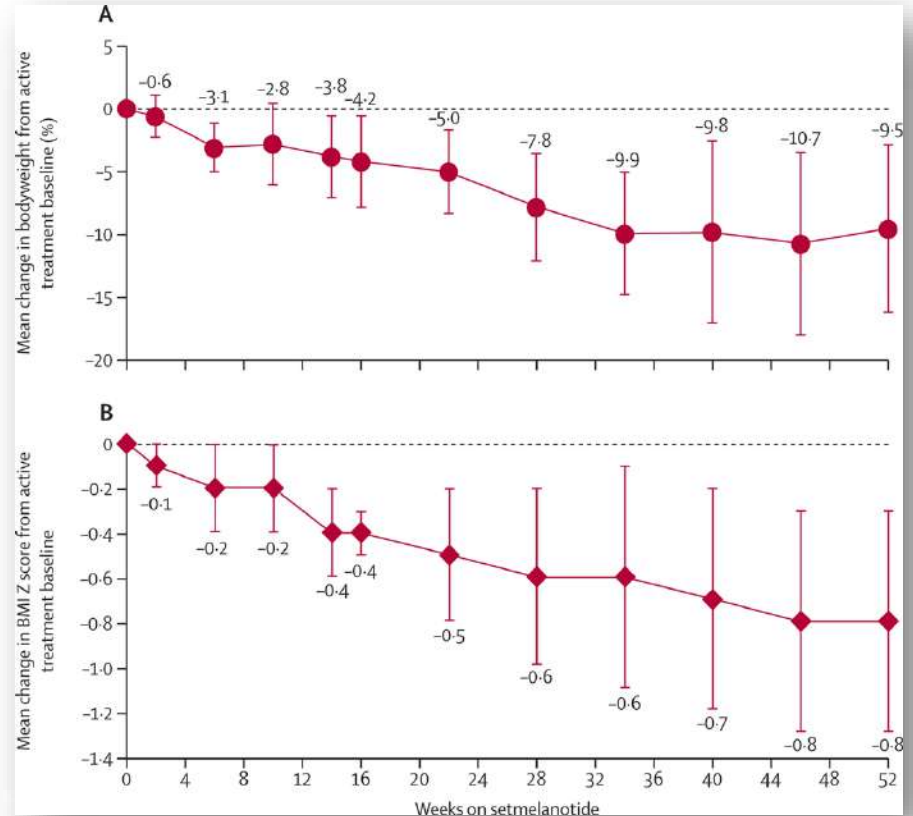


Setmelanotide interagisce con le alterazioni del pathway di MC4R contribuendo al trattamento dell'obesità di origine ipotalamica genetica o acquisita

Setmelanotide in pazienti con sindrome di Bardet-Biedl e sindrome di Alström



- Il 32,3% dei pazienti ha raggiunto una riduzione del peso corporeo di almeno il 10% dopo 52 settimane di setmelanotide



Obesità monogeniche

Iperfagia e obesità precoce

Obesità grave ≤ 5 anni

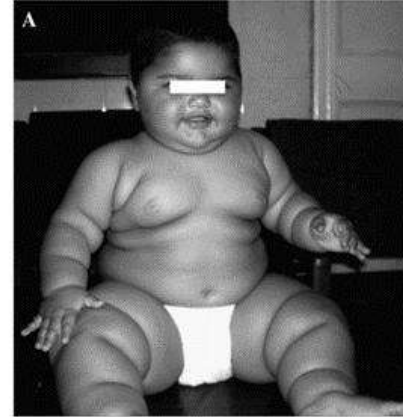
Consanguineità fra genitori

Peso normale nei genitori

Possibili deficit ipofisari

- **Deficit di Lep o LepR**
- **Deficit di POMC**
- **Deficit di PCSK1**
- **Deficit di MC4R**
- Deficit di SH2B1
- Deficit di GNAS
- Deficit di CPE
- Deficit di NCOA1

POMC-expressing neuron



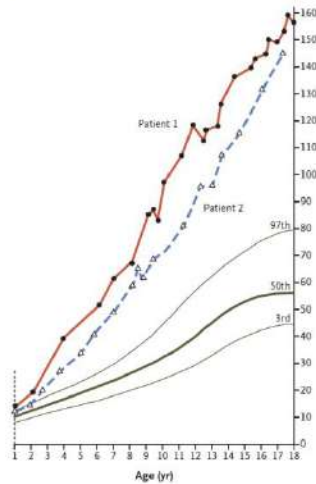
AGRP-expressing neuron



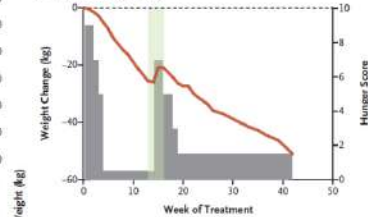
Setmelanotide riduce la fame e il peso nei pazienti con deficit di POMC o LEPR

Deficit di POMC

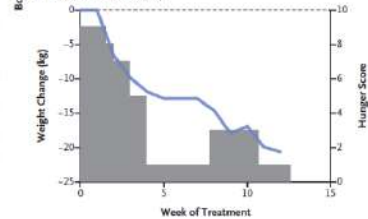
A Pretherapy Weight of the Two Patients



B Patient 1 during Therapy



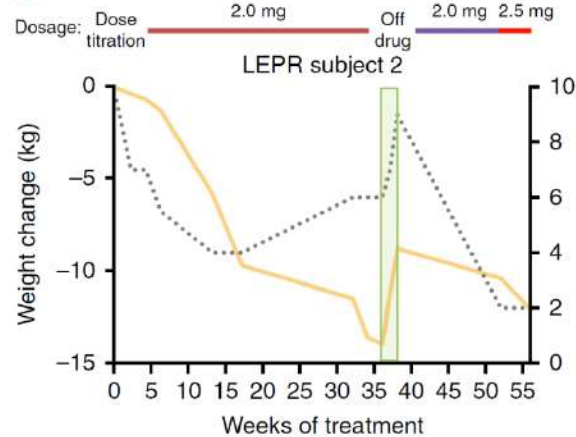
C Patient 2 during Therapy



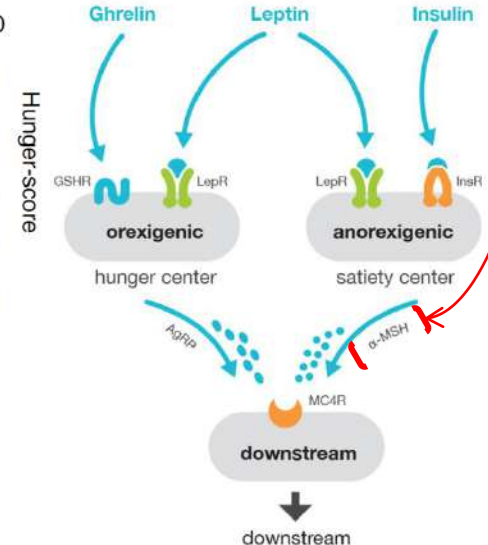
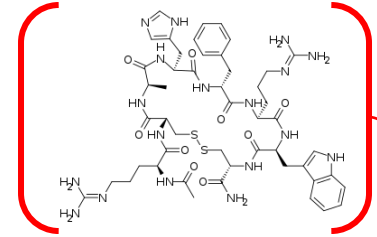
Kuhnen et al. N Engl J Med 2016

Deficit di LEPR

d



Clement et al. Nat Medicine 2018



Obesità ipotalamica (su base organica)

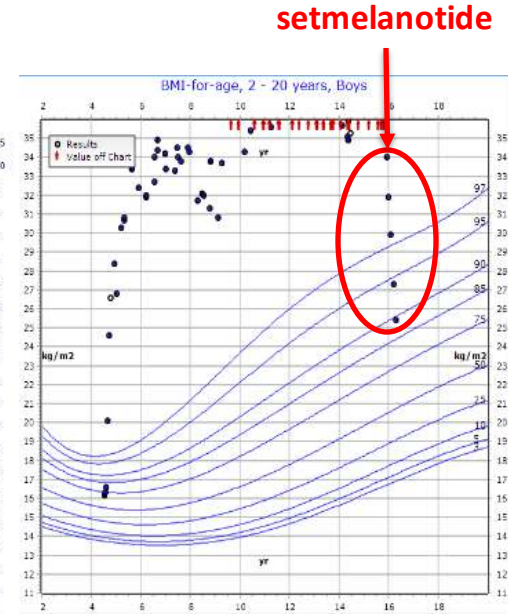
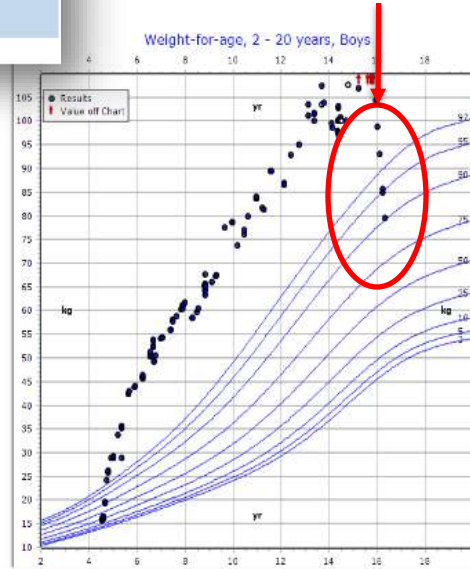
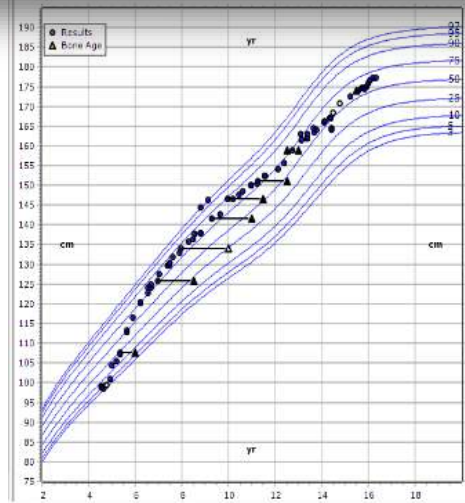
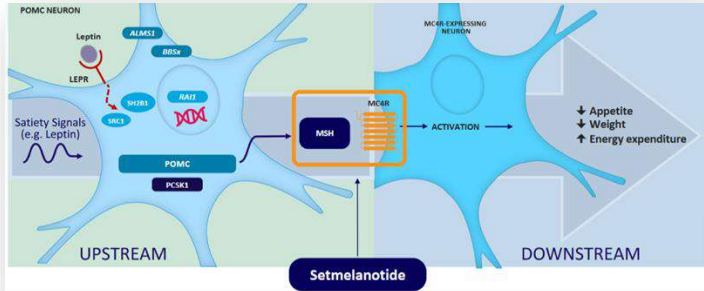
**Bassa attività fisica e dispendio energetico,
scarse prestazioni neurosensoriali**



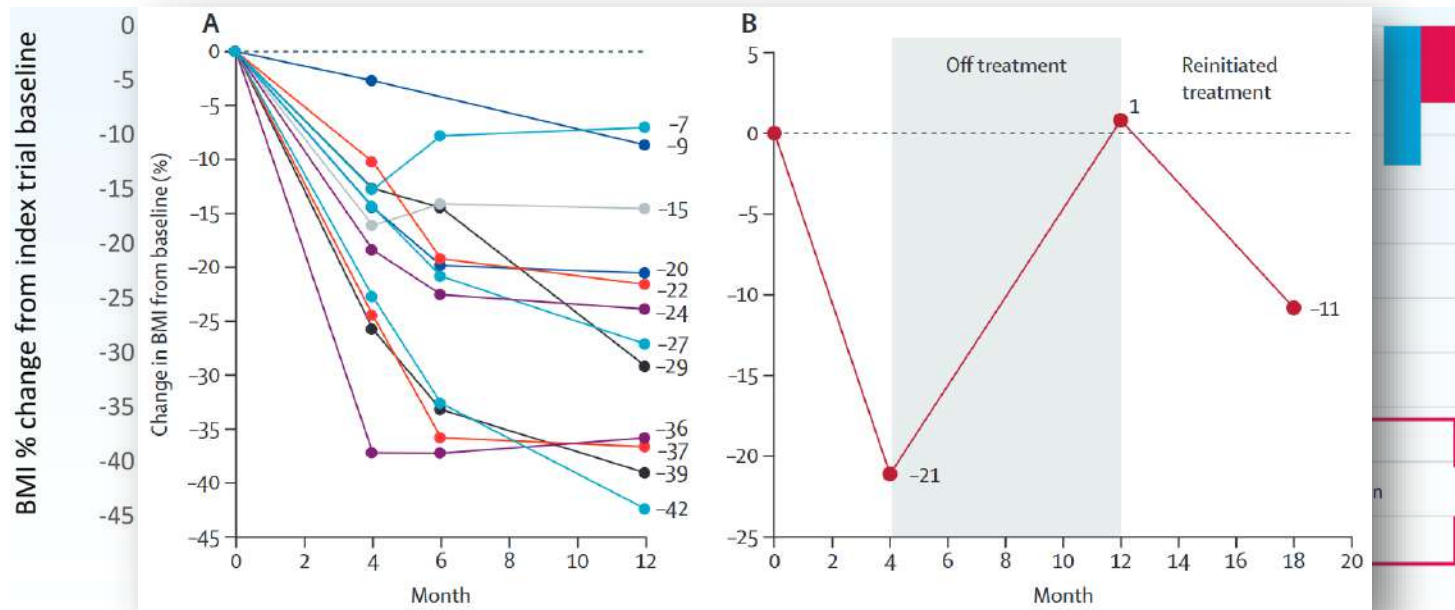
Interessa il 20% pre-diagnosi e fino
al 70% dei casi curati per
craniofaringioma



Setmelanotide nell'obesità ipotalamica



Setmelanotide in pazienti con obesità ipotalamica



1-3 mg/d

Roth CL, Scimia C, Shoemaker AH, Gottschalk M, Miller J, Yuan G, Malhotra S, Abuzzahab MJ. Setmelanotide for the treatment of acquired hypothalamic obesity: a phase 2, open-label, multicentre trial. *Lancet Diabetes Endocrinol.* 2024 Jun;12(6):380-389. doi: 10.1016/S2213-8587(24)00087-1. Epub 2024 Apr 30. PMID: 38697184.

Azioni extra-ipotalamiche degli incretino-mimetici

La capacità di influenzare l'assunzione di cibo, la motivazione e la preferenza alimentare è mediata dalla riduzione dei livelli di dopamina dopo l'attivazione di LSc

GLP-1R expression, mice

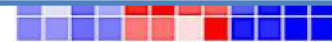
Accesso di semaglutide/liraglutide alle aree cerebrali

- I recettori di GLP-1 e GIP sono espressi in diverse aree del cervello, comprese le aree che sono correlate al sistema di ricompensa (nucleus accumbens, insula, putamen) e al rombencefalo.
- In caso di danno a carico delle strutture ipotalamiche medio-basali (ARC e PVN), i GLP-1RA e GIP-RA interagiscono direttamente e indirettamente con recettori siti nel rombencefalo e al di fuori delle strutture ipotalamiche.

Sema

GLP-1R

semaglutide⁷⁵⁰



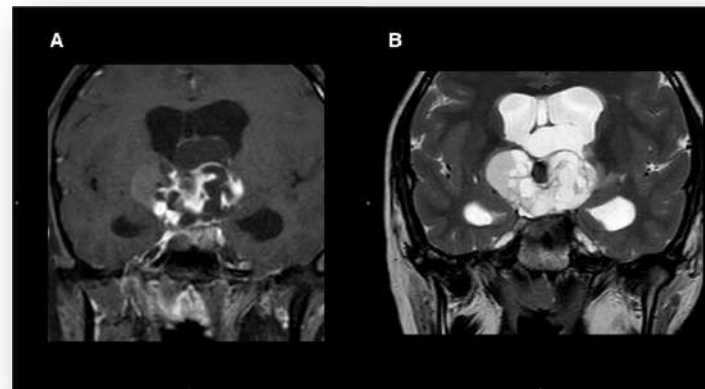
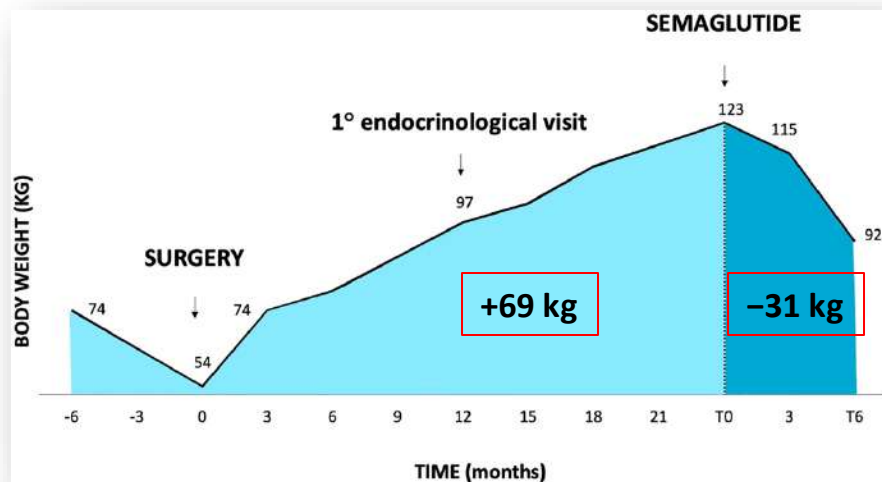
Low High



nucleus accumbens;
R, GLP-1 receptor;
teral septal nucleus;
ventral tegmental

Semaglutide for Treating Obesity Induced by Craniopharyngioma Resection: A Successful Case Study

Cristina Sciacovelli,^{1,2} Ginevra Moschione,^{1,2} Silvia Garelli,¹ and Uberto Pagotto^{1,2}



Questionnaire	Before semaglutide	6 months after semaglutide
Binge eating disorder ^a	39	9
Cognitive restraint of eating ^b	10	6
Disinhibited/uncontrolled eating ^c	14	6
Hunger ^d	13	1

^aBinge Eating Disorder Scale: <17 improbable, 17-27 possible, >27 probable.

^bThree-Factor Eating Questionnaire: >11 indicative of restraint.

^cThree-Factor Eating Questionnaire >8 indicative of disinhibition.

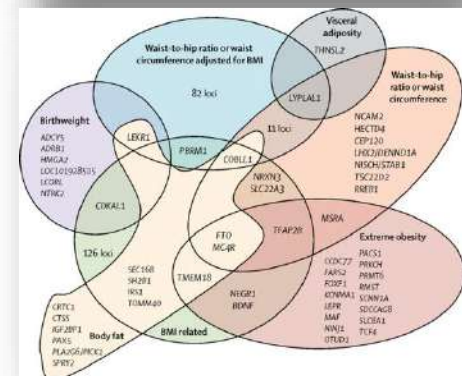
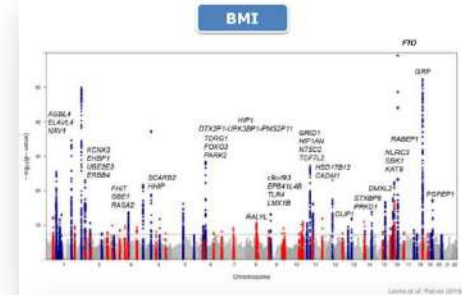
^dThree-Factor Eating Questionnaire >7 indicative of hunger.

Quali terapie nell'obesità poligenica

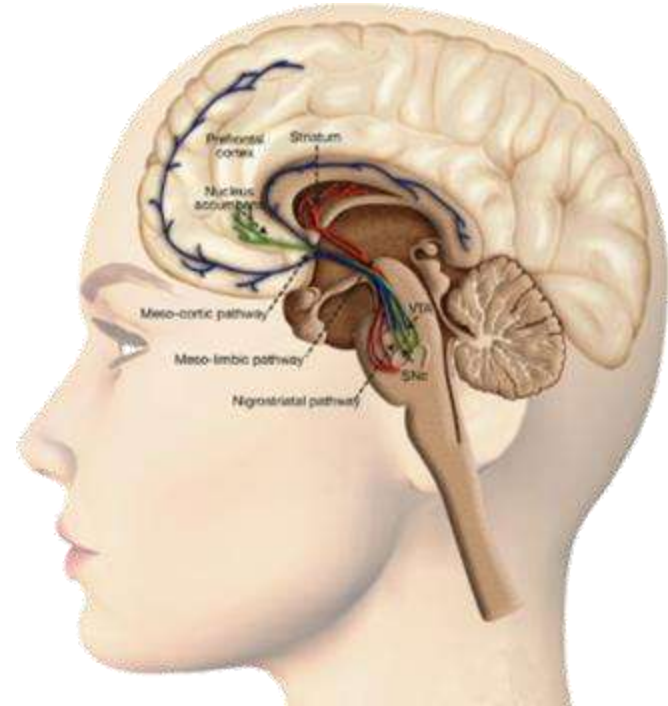
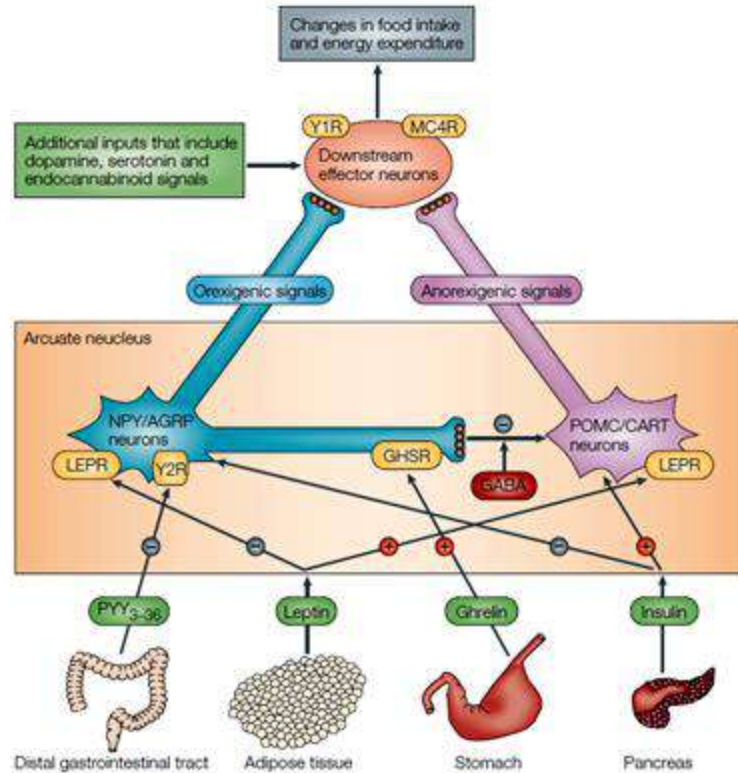
È il tipo più comune di obesità.

È causata dagli effetti combinati di più geni, ciascuno con un effetto piccolo ma cumulativo.

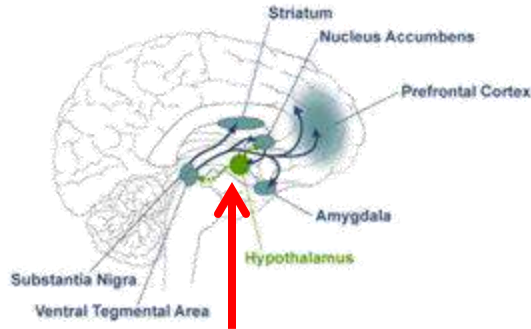
Origina dall'interazioni delle varianti geniche con fattori comportamentali e/o ambientali (ad. es., comportamento alimentare, attività fisica, stress).



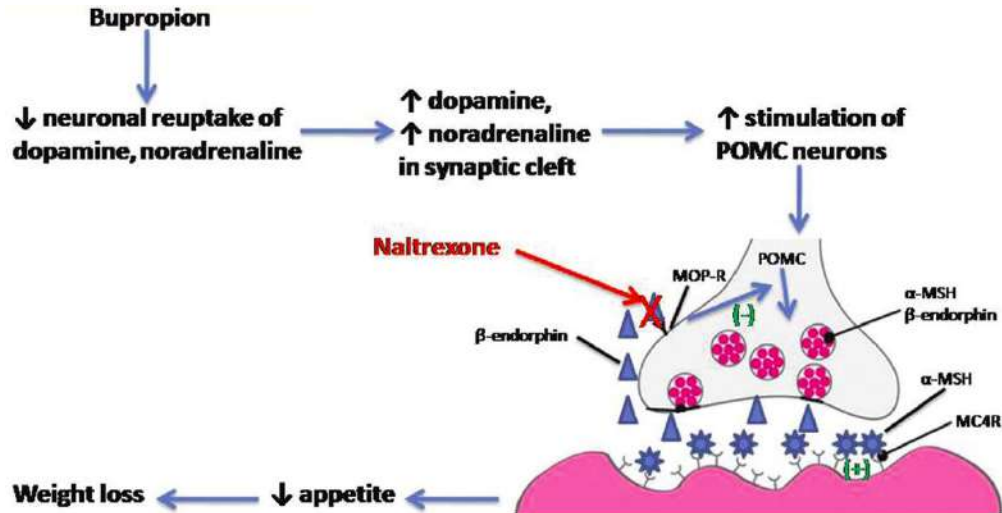
Controllo neurale dell'assunzione di cibo e gratificazione edonistica



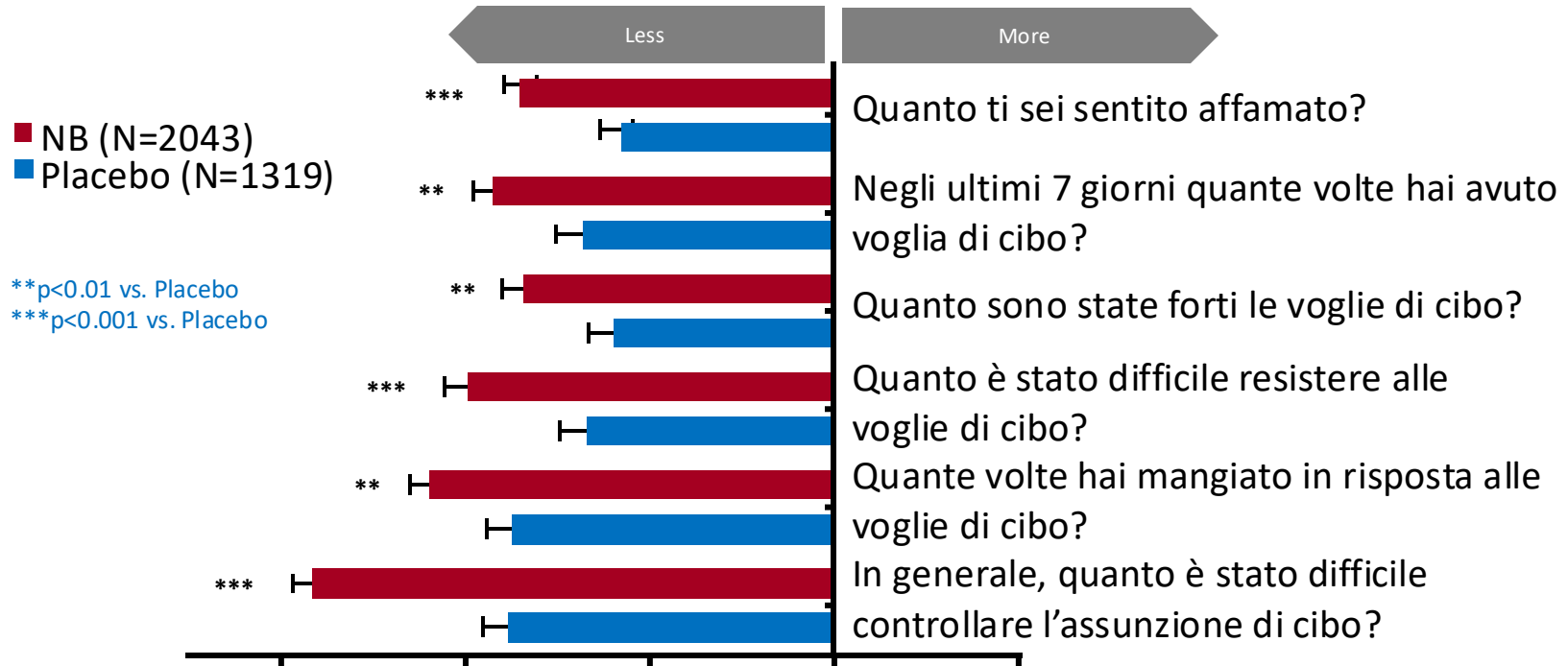
Naltrexone SR / Bupropione SR



N/B riduce l'appetito attivando i neuroni ipotalamici POMC⁺ e riducendo il desiderio di cibo attraverso un'azione sul sistema di ricompensa



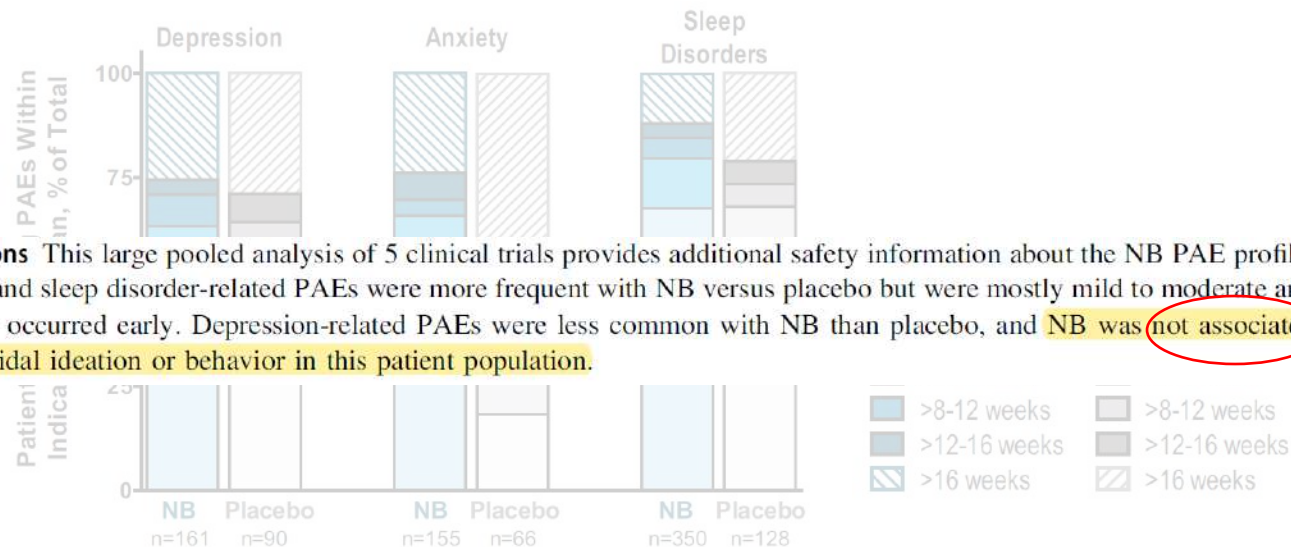
Naltrexone/bupropione migliora alcuni indici di controllo di comportamento alimentare





Psychiatric adverse events and effects on mood with prolonged-release naltrexone/bupropion combination therapy: a pooled analysis

Xavier Pi-Sunyer¹ · Caroline M. Apovian² · Susan L. McElroy³ · Eduardo Dunayevich⁴ · Lisette M. Acevedo⁵ · Frank L. Greenway⁴



Fenotipizzazione funzionale dell'obesità

Meccanismi fisiopatologici per ciascun sottotipo?

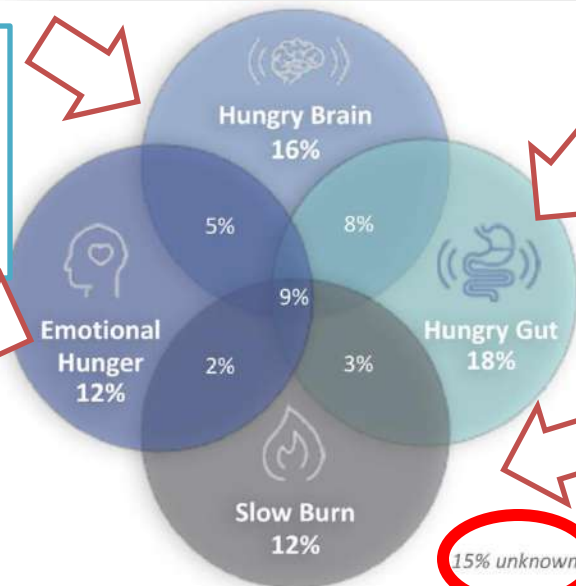
Fame (VAS)	Saziamento (Buffet)	Sazietà (VAS)	Svuotamento gastrico ($T_{1/2}$)	Alim. Edonica (HADS e TFEQ-21)	Spesa energetica (Cal. Ind. e HB)	Attività motoria (Contapassi)	Composizione (DXA)
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Necessità di maggiori calorie per raggiungere sazietà

- Alterata regolazione ipotalamica della fame/sazietà
- Resistenza alla leptina con ridotta segnalazione di sazietà
- Iperattività di NPY
- Deficit di α -MSH a livello di ARC

Comportamento edonico

- Iperattività sistema limbico
- Ridotta attività cort. prefrontale
- Squilibri nei sistemi dopaminergico e serotoninergico
- (Elevati livelli di cortisolo da stress cronico)



Breve sazietà, svuotamento gastrico rapido

- Accelerato svuotamento gastrico
- Ridotta produzione post-prandiale di GLP-1 e PYY
- Alterata segnalazione vagale della distensione gastrica
- Disbiosi del microbiota intestinale

Rallentamento del metabolismo basale

- Ridotta termogenesi di BAT
- Polimorfismi del gene FTO e altri geni metabolici
- Disfunzione mitocondriale nel muscolo scheletrico
- Adattamento post-dimagrimento

Farmacoterapia basata sulla classificazione del fenotipo obeso

- **cervello affamato**: fentermina-topiramato a rilascio prolungato alla dose di 7,5/46 mg al giorno o lorcaserina a 20 mg al giorno;
- **fame emotiva**: naltrexone/bupropione orale alla dose di 16/180 mg due volte al giorno;
- **intestino affamato**: liraglutide 3,0 mg;
- **combustione lenta**: fentermina 15 mg al giorno più aumento dell'allenamento di resistenza.

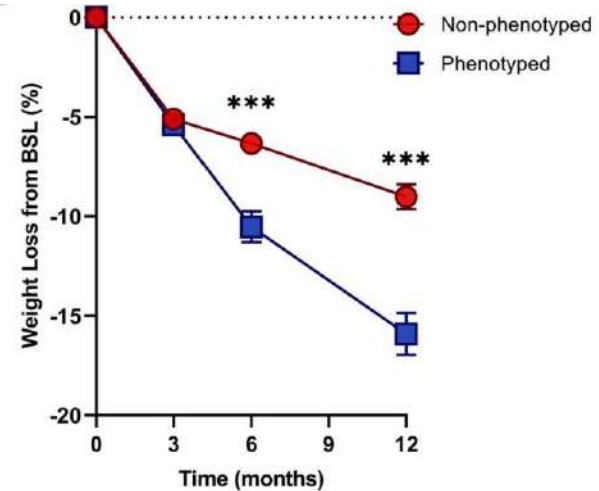
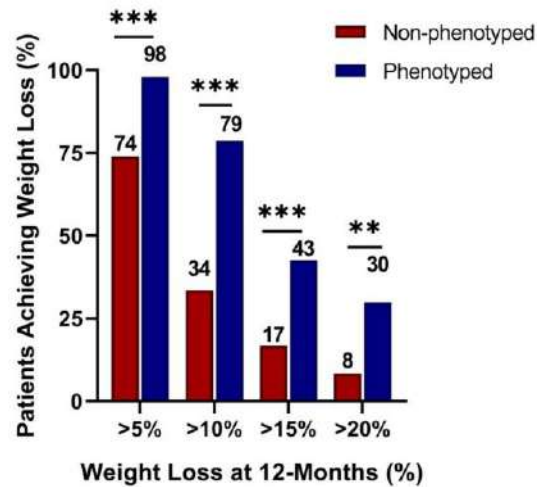
Fentermina: simpaticomimetico indiretto (aumento NA, DA e 5HCT)

Topiramato aumenta l'attività del GABA e inibisce l'attività del glutammato

Lorcaserina: agonista del recettore della serotonina 2C

Farmacoterapia basata sulla fenotipizzazione dell'obesità

- L'approccio guidato dal fenotipo è risultato associato a una perdita di peso 1,75 volte maggiore dopo 1 anno.
- La percentuale di pazienti che hanno perso >10% a 1 anno è stata del 79% rispetto al 34% con trattamento non guidato dal fenotipo



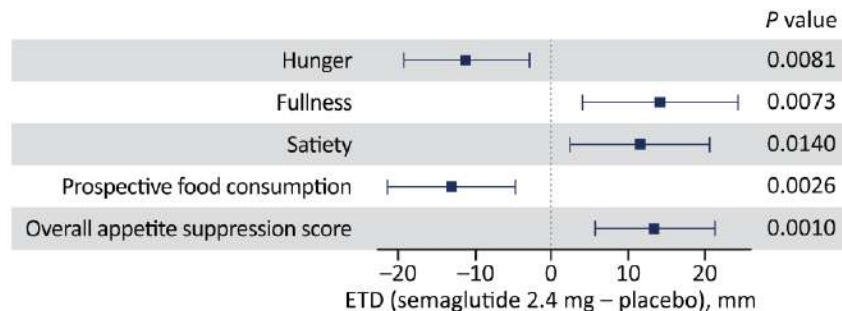
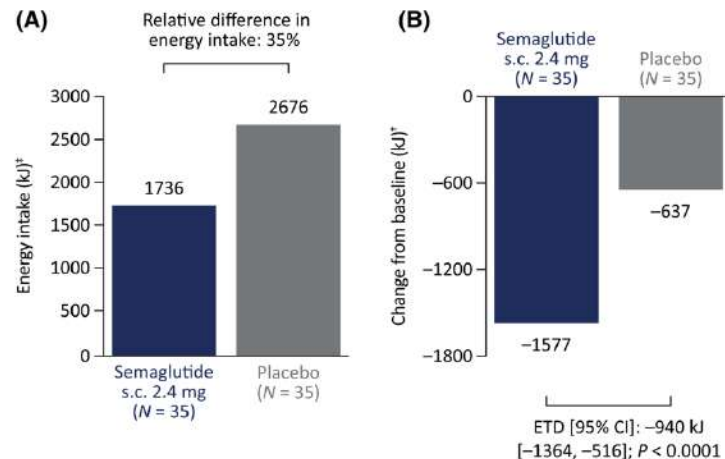
La categorizzazione spiega perché farmaci come i GLP-1RA mostrano maggior efficacia nei large eaters mentre interventi sulla modulazione dopaminergica (es. naltrexone/bupropione) risultano più appropriati nell'emotional eating.

The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity

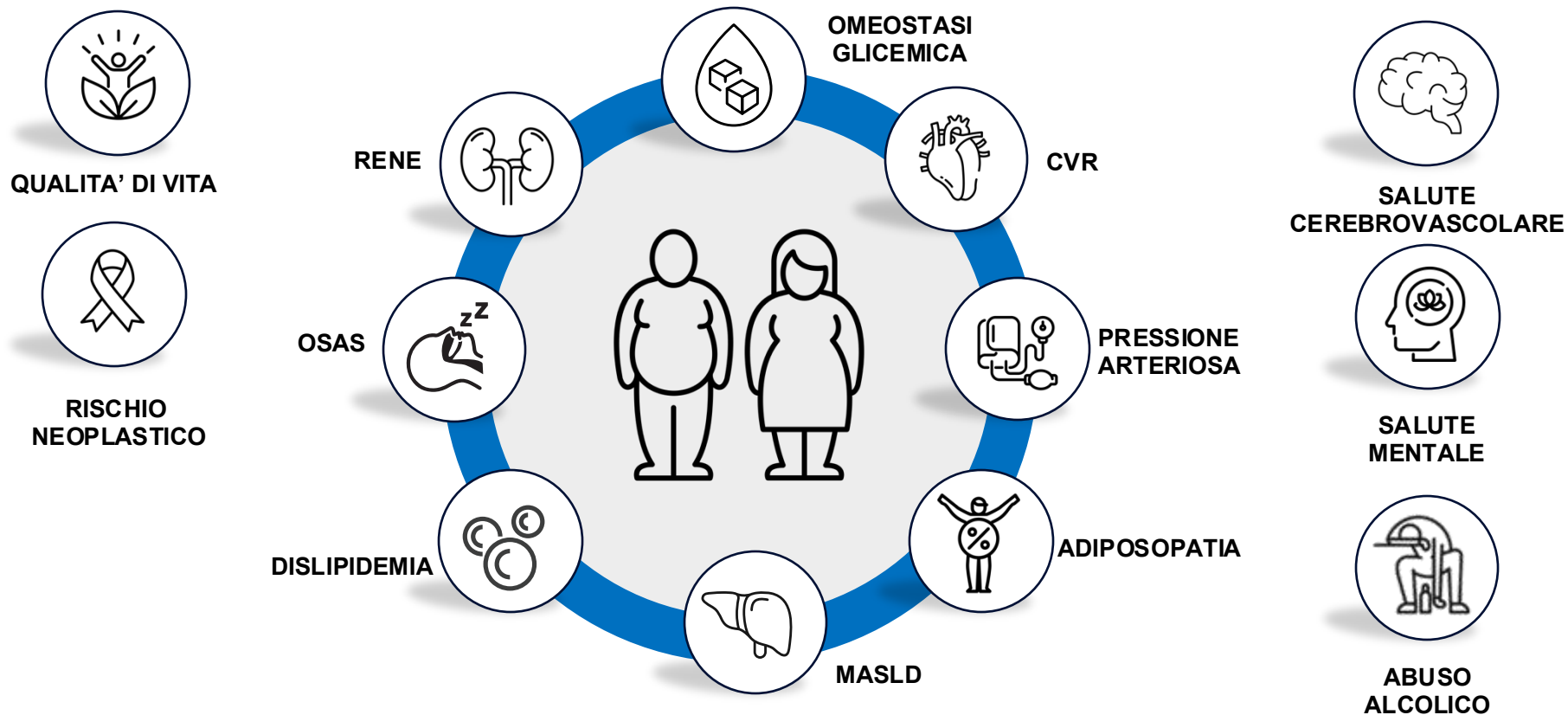
Martin Friedrichsen PhD¹ | Astrid Breitschaft MD² | Sayeh Tadayon MD¹ |
Alicja Wizer PhD¹ | Dorthe Skovgaard MD¹

Semaglutide 2,4 mg

- sopprime l'appetito e migliora il controllo dell'intake calorico
- riduce il desiderio di cibo e l'assunzione ad libitum rispetto a placebo
- (in alcuni studi riduce i punteggi della Binge Eating Scale)

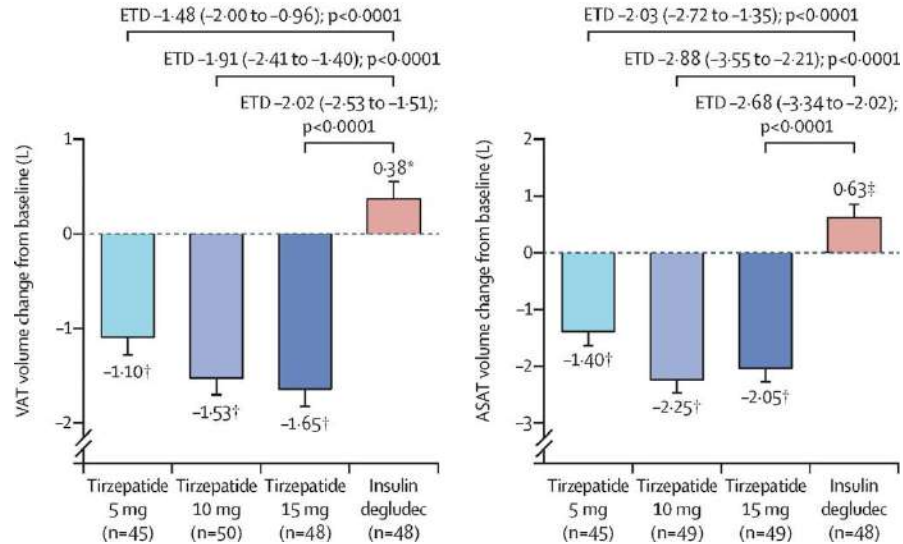
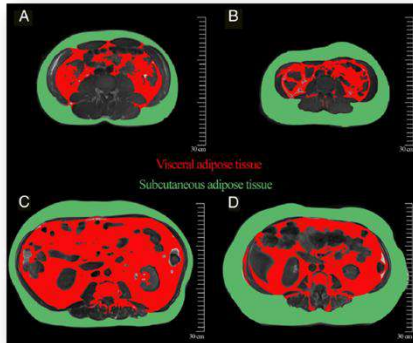
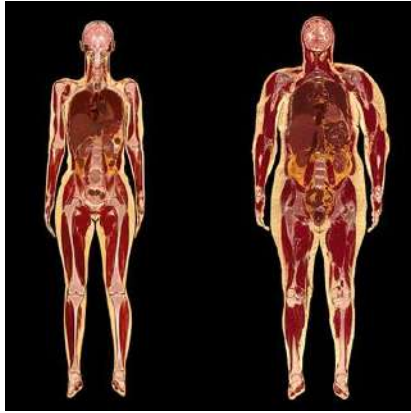


Benefici multi-sistemici degli agonisti incretinici



Tirzepatide migliora la distribuzione adiposa

SURPASS 3-MRI: 296 soggetti con T2D sottoposti a risonanza magnetica

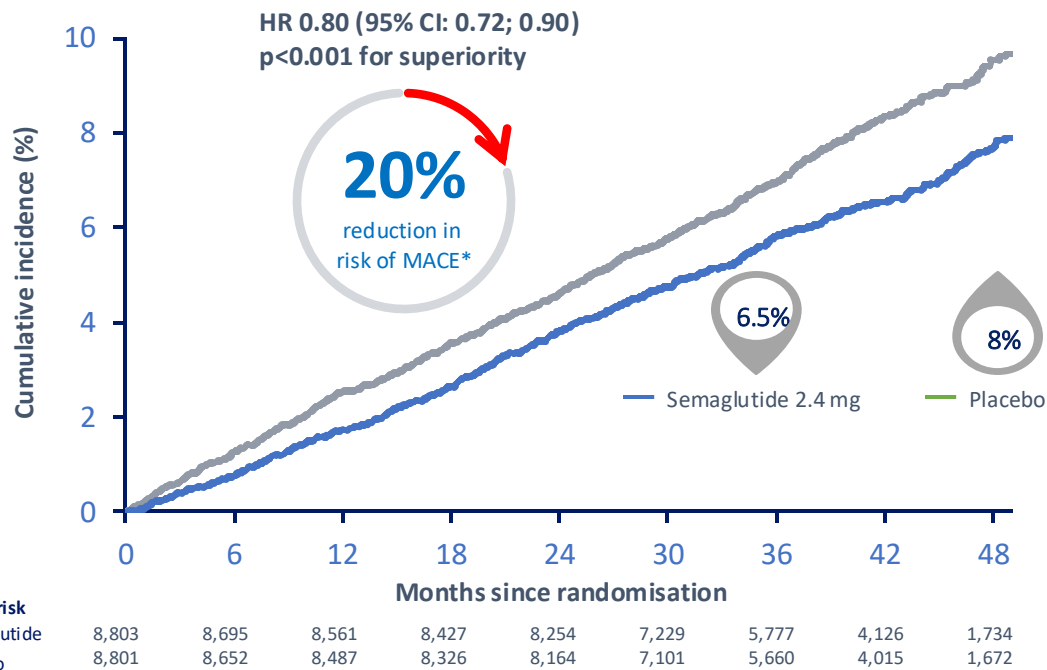


	Tirzepatide 5 mg (n=71)		Tirzepatide 10 mg (n=79)		Tirzepatide 15 mg (n=72)		Insulin degludec (n=74)	
VAT:ASAT ratio percentage	Mean	p value	Mean	p value	Mean	p value	Mean	p value
Baseline	61.68 (1.11)	..	60.14 (1.08)	..	60.74 (1.11)	..	60.40 (1.04)	..
At week 52	58.72 (0.62)	..	55.76 (0.56)	..	56.35 (0.56)	..	61.78 (0.57)	..
Change from baseline at week 52; p value vs baseline	-2.00 (0.62)	p=0.0014	-4.96 (0.56)	p<0.0001	-4.36 (0.56)	p<0.0001	1.06 (0.57)	p=0.065

SELECT: Effetti cumulativi sul MACE nell'obesità

Endpoint composito primario

17,604 Persone con obesità e CVD accertate, senza T2D



-15% incidenza di morte CV

-18% incidenza di HF

**-19% incidenza di qualsiasi
causa morte**

**Effetto oltre la sola
perdita di peso**

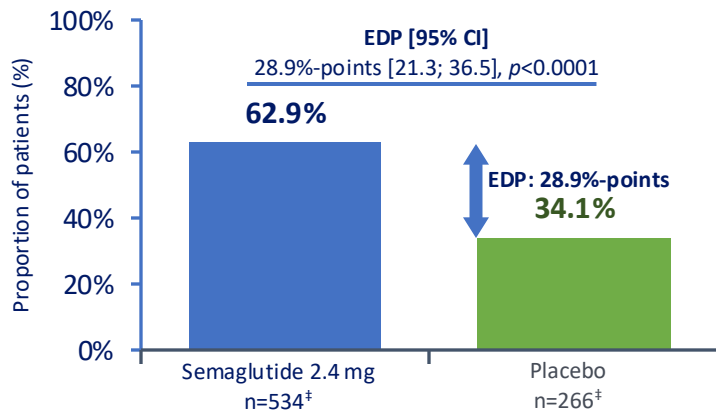
Cumulative incidence (using the Aalen-Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. American College of Cardiology, SELECT: Semaglutide Reduces Risk of MACE in Adults With Overweight or Obesity, Accessed October 2023, <https://www.acc.org/Latest-in-Cardiology/Articles/2023/08/10/14/29/SELECT-Semaglutide-Reduces-Risk-of-MACE-in-Adults-With-Overweight-or-Obesity>

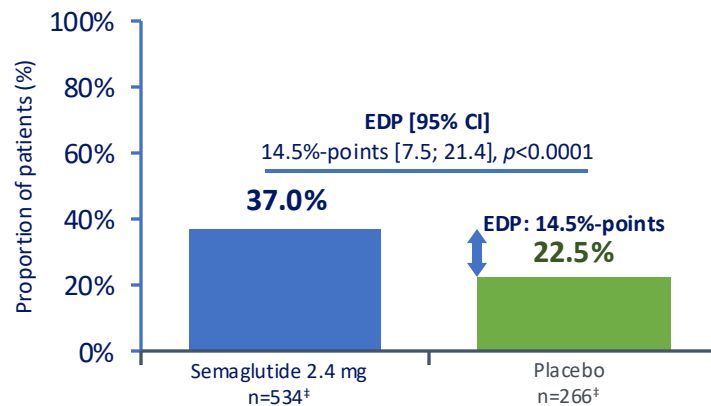
Semaglutide 2,4mg migliora MASH e fibrosi epatica

ESSENCE Trial: proportion of patients at Week 72

Risoluzione della MASH e nessun peggioramento della fibrosi epatica*



Miglioramento della fibrosi epatica e nessun peggioramento del MASH†

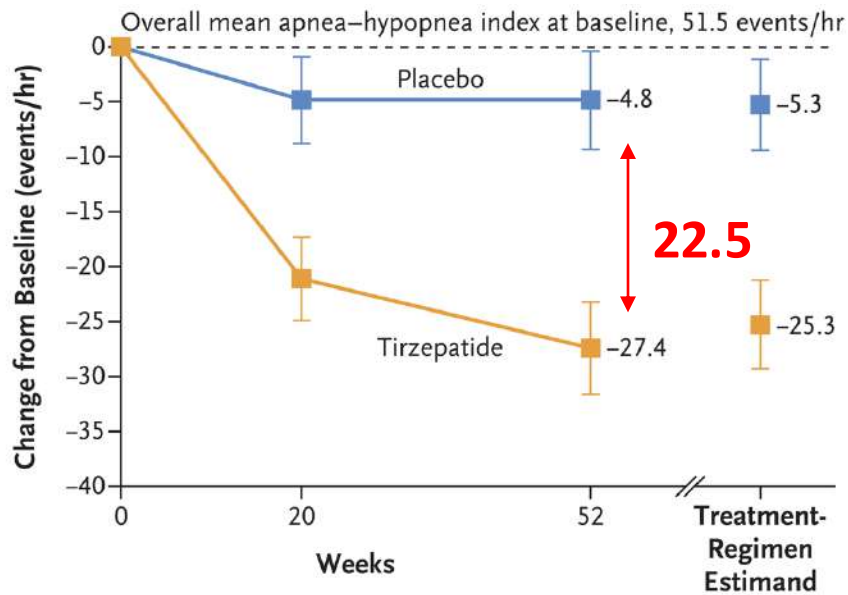


Analysis set: FAS (interim), first 800 randomised subjects. EDP: Estimated difference in responder proportions with 95% confidence interval and two-sided p-value. *Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. †Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. The absolute difference between responder proportions, 95% confidence interval, p-value was generated with the use of Cochran-Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). ‡Missing data were handled by reference-based multiple imputation and Rubin's rule based on the Mantel-Haenszel estimator and Sato's estimate of the standard error (reference) were used to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction associated steatohepatitis; NASH CRN, Non-Alcoholic Steatohepatitis Clinical Research Network. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting Late Breaker 5018; November 19 2024; San Diego, USA;

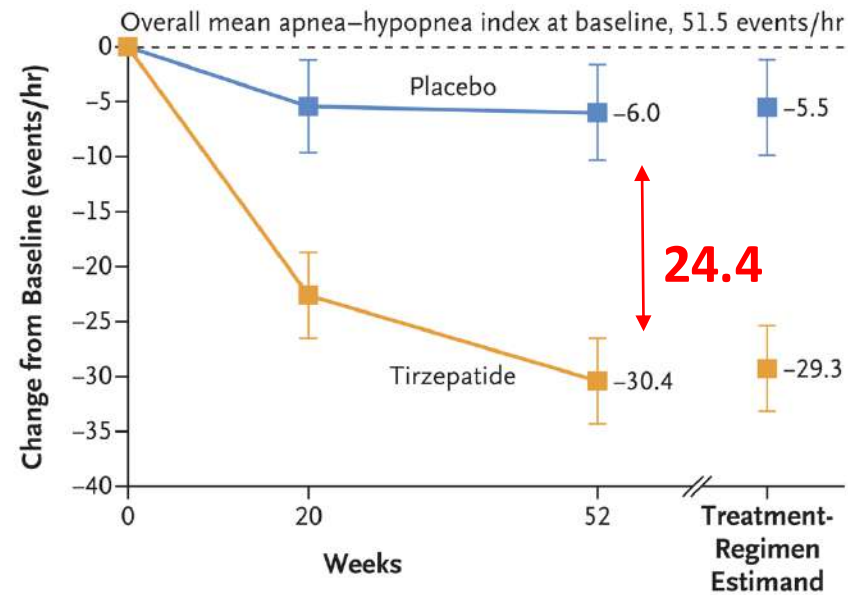
Tirzepatide migliora la gravità dell'OSA

SURMOUNT-OSA

Study 1: Partecipanti non in cPAP



Study 2: Partecipanti al cPAP



Concludendo...

- **PRESENTE**: NON esiste una Precision Medicine nell'obesità.
- Strategie centrate sulla causa
- Focus centrato sul paziente
- Effetti mirati alle complicanze
- **FUTURO**: farmaci multi-molecolari e approccio *gene-editing*.

